

Threats to global antimicrobial resistance control

Centrally approved and unapproved antibiotic formulations sold in India

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Structured summary

Introduction: Rising antimicrobial resistance (AMR) is a global health crisis. India has among the highest resistance rates and antibiotic consumption internationally. Extensive use of fixed dose combination (FDC) antibiotics and of unapproved formulations are claimed contributory factors but there has been no systematic examination of formulations or volumes sold.

Objective: To investigate the regulatory approval status and sales volumes of systemic antibiotics marketed in India.

Methods: This was an ecological study using regulatory records in India, the UK and US to determine the approval status in each country of systemic antibiotic FDC and single drug formulations (SDFs) marketed in India. Pharmatrac® sales data were used to determine the formulations and volumes sold in India (2007-2012), product numbers, and manufacturers.

Results: Of 118 systemic antibiotic FDC formulations marketed, 43(36%) were approved in India and 5(4%) in the UK and/or US. Almost half of formulations (58/118,49%) comprised dual antimicrobials, most unapproved in India, and many pharmacologically problematic. In contrast, 80/86(93%) SDFs were approved in India and over two-thirds in the UK and/or US.

Total antibiotic sales increased by 26% from 2056 Million-Units (2007-08) to 2583 Million-Units (2011-12). FDC sales rose by 38% *versus* 20% for SDFs. By 2011-12, FDCs comprised one-third of sales (872 Million-Units). Over one-third of FDCs sold (300.26 Million-Units, 34.5%) were unapproved. Multi-National Companies manufactured unapproved formulations and accounted for 19% of FDC and of SDF sales annually.

Conclusions: Sales in India of antibiotic FDCs, including unapproved formulations, are rising. In the context of increasing AMR rates nationally and globally, unapproved antibiotic FDCs undermine India's national AMR strategy and should be banned from sale.

What is known about this subject

- India has among the highest rates globally of antimicrobial resistance and of antibiotic consumption.
- Prescription medicines must have central regulatory approval before they can be marketed.
- Indian government reports claim extensive use of unapproved fixed dose combination (FDC) formulations of antibiotics.

What this study adds

- There were 118 antibiotic FDC formulations on the market in India (2007-2012) compared with 5 in the UK and US.
- Only forty-three of the 118 antibiotic FDC formulations (36%) had central regulatory approval; 75 (64%) were unapproved although the sale of unapproved new drugs is illegal in India.
- Multinational companies (MNCs) manufactured 53 of the 118 FDC formulations; only 33 (62%) of these were CDSCO-approved and 4 were MHRA/EMA- and /or FDA-approved formulations.
- Total antibiotic sales volumes increased by 26% from 2056 Million-Units (2007-08) to 2583 Million-Units (2011-12); FDC sales rose by 38% *versus* 20% for single drug formulations (SDFs).
- By 2011-12, FDCs comprised one-third of systemic antibiotic sales (872 Million-Units) but over one-third of FDCs sold (300 Million-Units, 34.5%) were unapproved.
- MNCs accounted for almost 20% of FDC and of SDF sales annually.

Introduction

Antimicrobial resistance (AMR) is an acknowledged global crisis but antibiotic consumption is rising despite access for many being poor.¹⁻⁴ In 2015, the World Health Assembly endorsed a five-point AMR global action plan⁵ and the World Health Organisation (WHO) has urged its adoption. For decades, the WHO has promoted rational medicines use and universal access through its Model List of Essential Medicines which acts as a guide for individual national lists of essential medicines (NLEMs).⁶ The WHO classifies antibiotics in ascending order of priority; important, highly-important, critically-important, and 'highest-priority-critically-important'.⁷ 'Highest-priority-critically-important' antibiotics are those where loss of efficacy due to resistance would have major impact on human health owing to high numbers of people affected by infections where they are the sole or one of few effective treatment. They include 3rd/4th generation cephalosporins, fluoroquinolones, glycopeptides, and macrolides.

During 2000-2010, antibiotic sales across 71 countries rose by 36%.⁸ Five countries (Brazil, China, India, Russia, South Africa) accounted for 76% of the increase. Consumption *per capita* was highest in India, a major producer of antibiotics with a fragile health system and among the highest rates globally of AMR.^{2,8,9} Parliamentary investigations have highlighted failures of its drug regulatory system including approvals of 'irrational' fixed dose combination (FDC) formulations of antibiotics and marketing of FDCs unapproved by the national regulator, the Central Drugs Standard Control Organisation (CDSCO), despite the sale or supply of unapproved new drugs being unlawful in India.¹⁰⁻¹⁶ The availability of FDCs '*not approved anywhere in the world*' has been criticised and a recommendation made that such formulations '*may not be cleared for use in India unless there is a specific disease or disorder prevalent in India, or a very specific reason backed by scientific evidence and irrefutable data applicable specifically to India that justifies the approval of a particular FDC.*'^{10,Para 9.8} However, no systematic examination was conducted of antibiotic FDCs available in India or of their approval status.

Fixed dose combinations

FDCs are formulations comprised of two or more drugs combined in a fixed ratio of doses and available in a single dosage form. Some antibiotic FDCs are comprised of an antibiotic plus non-antibiotic drugs, for example, amoxicillin, a beta-lactam antibiotic, plus clavulanic acid, an inactivation inhibitor.¹⁷ Others include dual antimicrobials, for example, trimethoprim+sulfamethoxazole.¹⁸ Dual antimicrobial FDCs are appropriate in well-defined situations where a particular combination is of proven efficacy, doses are stable throughout treatment, and the drugs have compatible pharmacological characteristics. Dual antimicrobial FDCs are to be distinguished from the concomitant use of two antibiotics as single drug formulations (SDFs). While infection treatment guidelines recommend two antibiotics in some situations, the antibiotics and their doses vary depending on epidemiological, host, and drug factors, and they are prescribed as SDFs.¹⁹⁻²⁴

Evaluating drug consumption in India

The AMR global action plan⁵ urges improved surveillance of antimicrobial use, but for many countries, including India, this is challenging. Studies using antibiotic sales data as a proxy for use have demonstrated rising sales of individual antibiotics and pharmacological groups but did not report the formulations sold or their approval status.^{1,8,25,26} We therefore analysed systemic antibiotic sales in India during a five-year period, 2007-2012, according to formulation (FDC or SDF) and approval in India and two other countries, the United Kingdom (UK) and the United States of America (US). We determined if formulations were NLEM-India-listed, if they included 'highest-priority-critically-important' antibiotics,⁷ and if they were manufactured by multi-national pharmaceutical companies (MNCs) as well as by Indian companies.

Aim

To examine the systemic antibiotic formulations sold in India in the context of their regulation and governance for licensing and to determine if these formulations were approved in the UK and/or the US.

Objectives

- To identify the FDC and single drug formulations on the Indian market, determine their regulatory approval status in India, the UK and the US and their NLEM-India listing.
- To examine 12-monthly sales trends (2007-2012), identify the top-selling antibiotic formulations (2011-12), and determine sales of WHO-designated 'highest-priority-critically-important' antibiotics categorised in each case according to approval.
- To determine the numbers of branded products on the market and manufacture by multi-national companies (MNCs).

Methods

This was an ecological study quantifying systemic antibiotic sales in India during 2007-2012 and including a cross-sectional analysis of the individual formulations sold in 2011-12.

Data sources

i) Drug sales data were obtained from PharmaTrac®, a commercial database of Indian pharmaceutical sales.²⁷ The data comprised monthly sales audits collected through multiple routes (some 5,000 pharmaceutical companies, 18,000 distributors/stockists, 32,000 sub-stockists, 500,000 retailers and hospitals, and dispensing doctors in 23 regions of India). The audits captured 35% of national sales and were projected to estimate total national sales. The data included formulation composition, generic and branded product names, manufacturers, sales volumes and value, and date of market launch. Sales volumes were reported monthly in units (a strip of ten tablets/capsules or one bottle (liquid formulations) for oral drugs or one injection for parenteral drugs). Formulations were coded according to therapy type and treatment group. For example, the FDC ceftriaxone+vancomycin, J1D42, was an anti-infective in the cephalosporin group of systemic anti-bacterials.

ii) Approvals in India: The CDSCO website published approvals for FDCs from 1961–2014 and for SDFs from 1971-2011.²⁸⁻³⁰ Listed chronologically, they included formulation content, indication, and approval date. We assumed CDSCO records were complete. State drug authority records of licenses granted for drug manufacture/distribution/sale were unavailable.

iii) Approvals in the UK and USA: The Medicines and Healthcare Products Regulatory Agency (MHRA) and/or European Medicines Agency (EMA) and Food and Drug Administration (FDA) websites were used to determine the approval status in the UK and US respectively of antibiotic formulations sold in India.³¹⁻

iv) NLEM-India: The 2011 list was used to determine the antibiotics recommended for use in India by a core committee of experts from the Ministry of Health and Family Welfare during the period of the cross-sectional analysis of sales, 2011-2012.⁶

Data Extraction

We examined PharmaTrac® data for the period October 2007 to November 2012. Systemic antibiotic formulations were identified independently by two people (PMcG, ABK). Information was extracted in duplicate onto Excel® spreadsheets. Discrepancies were resolved by consensus. We excluded anti-tuberculosis and primary anti-fungal or anti-viral formulations. We categorised systemic antibiotics according to FDC and single drug formulations. We subdivided FDCs into formulations comprising 1) dual antimicrobials, for example, two antibiotics or one antibiotic plus an anti-protozoal or anti-viral agent, or 2) one antibiotic plus other agents, for example, amoxicillin plus clavulanic acid, a beta lactamase inhibitor. Although they have some anti-microbial activity, we did not consider beta lactamase inhibitors as antibiotics in their own right because they are not used as antibiotic monotherapy and therefore we did not count these combinations as dual antimicrobials. We counted the numbers of brand-named products arising from each formulation, numbers of manufacturers and whether the manufacturer was Indian or a MNC. We summed monthly sales volumes (in millions of Units) to examine sales during five 12-month periods from October 2007-November 2012 where one Unit was a strip of ten oral tablets or capsules or one injection vial or one bottle of oral medicine.

Formulations were further categorised by CDSCO, MHRA/EMA and FDA approval status, and by NLEM-India listing. For approvals, we focused on the first approval granted. A formulation was deemed “approved” if ever recorded in the regulators’ lists of approved medicines, irrespective of dose amount

or modified release variations, and “unapproved” if it was not included. We adhered to STROBE-AMS guidelines for reporting.³⁴

Results

1. FDC and single drug formulations marketed in India, their regulatory approval status in India, the UK and the US and NLEM-India listing

FDC and single drug formulations marketed: There were 132 systemic antibiotic FDC formulations listed in PharmaTrac; 118/132 FDCs specified the full formulation permitting regulatory approval to be determined ('known formulations', Table 1); 13/132 FDCs were described as 'combinations' naming the antibiotic but not other formulation components. 'Combinations' comprised <1% of antibiotic sales in 2011-12 (Supplementary_Table). The study analyses are based on the 118 'known formulations'. There were 86 SDF antibiotics listed in PharmaTrac.

Regulatory approval status in India, the UK and US

FDCs: Of the 118 FDC formulations, 43(36%) were CDSCO-approved and 75(64%) had no record of approval; 4(3.4%) were approved In the UK and US; 2(2%) were NLEM-listed (Figure 1).

Sixty FDC formulations (60/118, 51%) comprised one antibiotic plus agents including beta-lactamase inhibitors, lactobacillus, mucolytics, and secretolytics. Of these, 28/60(47%) were CDSCO-approved, 32/60 (53%) had no record of approval and 3/60 (5%) were approved by the MHRA/EMA and/or FDA (amoxycillin+clavulanic acid, piperacillin+tazobactam, imipenem+cilastatin) (Supplementary_Table_FDC118).

Fifty-eight FDC formulations (58/118, 49%) comprised dual antimicrobials: 36/58 were two antibiotics; 17, an antibiotic plus an anti-protozoal drug; and 5, an antibiotic with another antimicrobial (for example, anti-fungal, anti-viral) (Figure 1). Fifteen dual antimicrobial formulations (15/58, 26%) were CDSCO-approved and 43/58 (74%) were unapproved; one (trimethoprim+sulfamethoxazole) was

approved by the MHRA/EMA and FDA and one (ampicillin+cloxacillin) by the MHRA but not the FDA (Supplementary_Table_FDC118).

SDFs: Of the 86 SDF antibiotics, 80 (93%) were or were likely to be CDSCO-approved (Figure 1): 62 had approval listed, six had CDSCO-granted European import licenses, two were NLEM 2011-listed and ten were discovered in the 1950's-1960's with approval possibly granted prior to 1971, the earliest CDSCO SDF approval record. Six SDFs (7%) had no record of CDSCO approval. Twenty-two SDFs (26%) were NLEM-listed, 57/86 (66%) were MHRA/EMA-approved, and 62/86 (72%) were FDA-approved (Figure 1).

2. Twelve-monthly sales trends during 2007-2012, approvals, top-selling formulations and 'highest-priority-critically-important' antibiotic sales, 2011-2012

Table 1 shows the systemic antibiotic 12-monthly sales volumes during the five years examined, November 2007-October 2012. Total systemic sales (FDCs+SDFs) increased by 26% from 2055.86 Million-Units in 2007-08 to 2583.07 Million-Units in 2011-12 with FDCs rising by 38%, SDFs by 20%. The FDC proportion of annual sales increased from 31% to 34% while the SDF proportion fell from 69% to 66% (Table 1).

FDC sales: In 2007-08, 53% of FDC sales were comprised of CDSCO-approved formulations (Table 1, Figure 2). By 2011-12, this had increased to 66%. Dual antimicrobials comprised 56% of FDC sales in 2011-12, most being unapproved formulations (Figure 2). In total, less than half of FDCs sales were of MHRA/EMA-approved and/or FDA-approved formulations and fewer than one-third were NLEM-listed (Figure 2).

SDF sales: Almost all SDF sales were of CDSCO-approved formulations, 97% in 2007-08 and 98% in 2011-12. Over 90% were MHRA/EMA-approved and/or FDA-approved and two-thirds were NLEM-listed (Figure 2).

Top selling formulations, 2011-12

FDCs: Amoxicillin+clavulanic acid was the top selling formulation followed by ampicillin+cloxacillin, trimethoprim+sulfamethoxazole, and ofloxacin+ornidazole. The twenty top-selling FDC formulations, listed in Table 2, comprised 61% of total FDC sales in 2011-12; 10/20 were dual anti-microbial formulations; 7/20 formulations had no record of CDSCO approval; 16/20 were unapproved by the MHRA/EMA and 17/20 were not FDA-approved; The two NLEM-listed FDCs (amoxicillin+clavulanic acid and trimethoprim+sulfamethoxazole) together accounted for 29% of sales in 2011-12.

SDFs: Ceftriaxone was the top-selling SDF followed by cefixime, metronidazole and cefotaxime. The twenty top-selling SDFs, listed in Table 3, comprised 87% of total SDF sales in 2011-12. All had or were likely to have CDSCO approval; all had MHRA/EMA approval; 19/20 had FDA approval. NLEM-listed SDFs made up 65% of SDF sales.

Highest-priority-critically-important antibiotic sales, 2011-12

FDCs: In 2011-12, 42% of FDC sales in India included WHO-designated 'highest-priority-critically-important' antibiotics (Supplementary_Table). Eight formulations were dual antimicrobial FDCs containing two of these antibiotics: azithromycin+ofloxacin, cefixime+azithromycin, cefixime+ofloxacin, cefpodoxime+azithromycin, cefpodoxime+levofloxacin, cefpodoxime+ofloxacin, ceftriaxone+vancomycin, levofloxacin+azithromycin. They made up 5% of FDC sales volumes in 2011-12.

Two formulations were CDSCO-approved (cefexime+ofloxacin, cefpodoxime+ofloxacin). None was FDA-approved, MHRA/EMA-approved or NLEM-listed.

SDFs: Among SDFs, 'highest-priority-critically-important' antibiotics comprised 54% of sales in 2011-12, carbapenems and polymyxins, 0.4% of sales.

3. Numbers of brand-named products and manufacture by MNCs

FDCs: The 118 FDC formulations gave rise to 3307 brand-named products made by 476 manufacturers of which 464 were India-based and 12 were MNCs. The FDCs with the greatest numbers of products were: ofloxacin+ornidazole, 382 branded products made by 279 manufacturers; amoxicillin+clavulanic acid, 293 products, 189 manufacturers; and ciprofloxacin+tinidazole, 208 products, 147 manufacturers (Supplementary_Table_FDCproducts).

MNCs manufactured 53/118 (45%) FDC formulations (Figure 1) (Supplementary_Table_FDC_products). These gave rise to 148 brand-named products manufactured by 12 MNCs including Abbott, Astra Zeneca, Baxter, Bayer, Eli Lilly, GlaxoSmithKline (GSK), Merck/MSD, Novartis, Pfizer, Sanofi-Aventis, and Wyeth. Twenty-eight MNC-manufactured formulations were dual antimicrobials; nineteen with two antibiotics (for example, ampicillin+dicloxacillin, ceftriaxone+vancomycin); nine with an antibiotic +anti-protozoal (for example, ciprofloxacin+tinidazole, ofloxacin+ornidazole) (Supplementary_Table_FDC_products).

Thirty-three MNC-manufactured formulations (33/53, 62%) were CDSCO-approved; 4/53(8%) were MHRA/EMA- and FDA-approved (amoxicillin+clavulanic acid, imipenem+cilastatin, piperacillin+tazobactam, trimethoprim+sulfamethoxazole). Of the 20 formulations without CDSCO approval, 18 were manufactured by Abbott. Other MNCs each manufactured 1-3 unapproved formulations (Supplementary_Table_FDC_products).

Of the eight formulations comprised of two 'highest-priority-critically-important' antibiotics, all were manufactured by Indian pharmaceutical companies and five were manufactured by Abbott but not by other MNCs.

SDFs: The 86 SDF antibiotics gave rise to 4934 branded products made by 532 manufacturers; 515 were India-based and 17 were MNCs. The antibiotics with the greatest numbers of products were: ofloxacin, 443 branded products made by 303 manufacturers; azithromycin, 370 products, 263 manufacturers; cefixime, 341 products; 228 manufacturers (Supplementary_Table_SDF_products).

MNCs manufactured 62/86 (72%) SDF formulations (Figure 1) (Supplementary Table_SDF_products).

These gave rise to 269 brand-named products manufactured by 17 MNCs. Fifty-eight MNC-manufactured SDFs (58/62, 94%) were CDSCO-approved/likely to be approved, 47/62 (76%) were FDA-approved and 44/62 (71%) were MHRA/EMA-approved (Figure 1).

MNC-manufactured antibiotic sales: MNC-manufactured FDCs and SDFs comprised approximately 19% of both FDC and SDF sales annually. Among the twenty top-selling FDC and SDF formulations, 90% and 100% respectively were MNC-manufactured (Tables 3 and 4).

Discussion

India was recently shown to be the largest consumer of antibiotics *per capita* among 71 countries and to have increasing levels of consumption.⁸ Our study demonstrates for the first time that its high consumption is led by rising sales of fixed dose combinations of antibiotics, the majority unapproved by the national drugs regulator, the Central Drugs Standard Control Organisation (CDSCO). It confirmed parliamentary committee observations that most FDCs available in India were unapproved by regulators elsewhere and in addition, found that multi-national companies were among those manufacturing unapproved FDC formulations.

Of 118 antibiotic FDC formulations on the market during 2007-2012, almost two-thirds had no record of CDSCO approval and only five were approved by UK and/or US regulators. In contrast, most of the 86 single drug antibiotic formulations on the Indian market were approved by the CDSCO and by UK and US regulators. Almost half of the FDC formulations included dual-antimicrobials, some combining two 'highest-priority-critically-important' antibiotics. India's national list of essential medicines included only two of the antibiotic FDCs and twenty-two of the SDFs marketed.

In the analysis of sales volumes, FDC sales increased by 38% over five years, 2007-2012, compared with 20% for single drug formulations. By 2011-12, antibiotic FDCs accounted for over one-third of total antibiotic sales. This is strikingly high. In comparison in the UK, 5% of community-dispensed systemic antibiotics in 2012 were FDCs, 95% were SDFs.³⁵ Though subject to no regulatory scrutiny, unapproved FDC formulations comprised more than one-third of the FDC sales annually in India.

SDFs accounted for two-thirds of total antibiotic sales volumes, almost all of which were CDSCO-approved formulations. Of these, two-thirds of sales were for NELM-listed antibiotics and over half were for 'highest-priority-critically-important' antibiotics.⁷ There were thousands of brand-named FDC and

SDF products on the market manufactured by several hundreds of Indian companies and fewer than twenty MNCs.

MNC manufacture in India of FDCs unapproved in the UK and US

MNCs manufactured almost 20% of the systemic antibiotic FDC and SDF volumes sold in India annually. Twenty MNC-manufactured FDC formulations had no record of CDSCO approval. Only four of the fifty-three FDC formulations made in India by MNCs had UK or US regulatory approval. The leading manufacturer was Abbott whose role in the manufacture of unapproved dual-antimicrobial FDC formulations has been criticised.³⁵⁻³⁷ In contrast to FDCs, most MNC-manufactured SDF formulations were CDSCO-approved and over 70% had UK/US regulatory approval. Pharmaceutical companies, including some manufacturers of unapproved FDCs, made a declaration in 2016 on their commitment to combating anti-microbial resistance.³⁸

Pharmacological problems of FDCs

Many dual antimicrobial formulations were pharmacologically poorly considered. Combinations of broad spectrum antibiotics with anti-protozoal drugs were among the most highly prescribed FDCs, for example, ofloxacin+ornidazole and norfloxacin+metronidazole. Used to treat diarrhoea, their intention is to cover possible bacterial and amoebic causes but as antimicrobials are not first-line diarrhoea treatment, the combinations are inappropriate and may exacerbate diarrhoea owing to their effects on normal gut flora.

FDC component drugs were commonly pharmacologically incompatible, having different half-life durations requiring different dosing frequencies that cannot be accommodated in FDC formulations. For

example, ofloxacin, dosed once daily, was combined with ornidazole or tinidazole both needing twice daily dosing or with metronidazole, needing 8-hourly dosing. Similarly, azithromycin (once daily) was combined with cefpodoxime (twice daily). Some combinations had potentially serious interactions. In the case of azithromycin+ofloxacin, both antibiotics are associated with prolongation of the cardiac QT-interval and together are potentially harmful for vulnerable individuals. Gatifloxacin was withdrawn by regulators including the FDA in 2006 owing to associations with glycaemic disorders but was available in combination with both ornidazole and metronidazole.

Drug regulatory weaknesses

Our study exposes consequences of acknowledged weaknesses in India's drug regulatory system. Though the government has convened reviews of regulation, actions to improve matters have been ineffective.^{10-13,39,40} In February 2016, the Kokate Committee, constituted 'for examining the safety and efficacy of unapproved FDCs which were licensed by State Drug Licensing Authorities without due approval of (the Drugs Controller General (India)) DCG(I)' published its report to government.¹³ Over 6000 brand-named products were examined, (including 163 systemic antibiotic FDC products) and categorised by the Committee as 'irrational', 'requiring further deliberation', 'rational' or 'requiring further generation of data'.⁴⁰ In March 2016, the government banned 344 FDC formulations from sale because none had 'therapeutic justification' and each was 'likely to involve risk to human beings whereas safer alternatives to the said drug are available'.⁴¹ Following appeals, the ban was overturned by Delhi High Court in November 2016.⁴² The matter continues with the Supreme court recently upholding the government's right to ban drugs in the public interest.⁴³ Included in the ban were sixteen unapproved systemic antibiotic FDC formulations listed in PharmaTrac. Of these, 11/16 were dual antimicrobials and 6/16 were manufactured by MNCs. In 2011-12, these 16 formulations accounted for

14% of antibiotic FDC sales. The government did not explain the selection criteria for banning. Many alternative approved formulations similar to those classed by the Kokate Committee as 'irrational' are available so even if the ban had been enforced, the impact on sales of antibiotic FDCs would be negligible.

In a further delay to improving regulation, the government announced in June 2016 that it was withdrawing the Drugs and Cosmetics (Amendment) Bill, 2013, introduced in the Rajya Sabha on 29.08.2013, and instead will 'comprehensively review the existing law with two fold objectives viz. to facilitate the ease of doing business and substantially enhancing the quality and efficacy of our products'.⁴⁴

Actions needed

The sale of unapproved, unscrutinised FDC antibiotics undermines measures to control antimicrobial resistance. Definitive regulatory action to ensure that antibiotic formulations sold in India are rigorously evaluated and approved by the drugs regulator would permit India to participate effectively in AMR control measures. A starting point would be a government ban on the sale and manufacture of unapproved antibiotic formulations, commencing with dual antimicrobial FDCs (Supplementary_Table). Centrally unapproved formulations of new drugs are illegal.¹⁵ This approach would not deprive patients of clinically-needed antibiotics because approved SDFs are available. In all cases, the evidence base supporting CDSCO systemic antibiotic approvals, both FDC and SDF, should be made publicly available. In relation to MNC-manufactured antibiotic FDCs, the MNCs should be required to justify the sale of products in India that do not have the approval of their own national regulators and in multiple cases, not even the approval of the Indian regulator. Enactment is poor in India of policies to reduce inappropriate antimicrobial use.⁴⁵ Work is needed to understand why prescribers are choosing anti-

microbial FDCs, not adhering to the NLEM, and frequently prescribing unapproved formulations. If these actions were implemented, India could participate effectively in the solutions proposed for national⁴⁶ and global action on resistance.^{1,23,47,48}

Limitations

We used publicly available CDSCO information to determine antibiotic approvals. We assumed records were accurate and cross-checked sources extensively but it is possible we overlooked information.

Pharmatrac® drug sales data are estimates determined using standard sampling methods. In common with similar data-sets, they do not distinguish prescription from non-prescription sale but with high levels of non-prescription antibiotic use in India, sales data provide the most accurate estimate of national antibiotic use. When we categorised the Pharmatrac® sales volumes by antibiotic class, the rankings matched those reported using another commercial datasource.^{8,49}

Conclusions

This systematic examination of Indian sales data and regulatory information confirms government claims about anti-microbial use. FDCs comprise increasing proportions of antibiotic sales but most of the formulations sold are unapproved by the CDSCO and only a handful are approved by regulators in the UK and US. Their manufacture by MNCs contradicts stated commitments on combating antimicrobial resistance. The use of unapproved, unscrutinised antibiotic FDC formulations is likely to contribute to India's rising antimicrobial resistance. Until definitive action is taken to ban most systemic antibiotic FDCs from manufacture and sale, AMR initiatives in India are likely to be undermined and the global action plan impeded.

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Transparency Declaration: None of the authors has Conflicts of Interest to declare

Ethics Committee approval: Ethics approval was not required – this is a study of commercial sales data and drug approval listings; No patients or patient data were included in the study.

Registration: This is not a clinical trial and is not registered on a clinical trial register.

Data Transparency: The data on which the work is based are provided in the Supplementary table

Patient involvement: No patients or patient data were involved in this study.

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Abbreviations

CDSCO	Central Drugs Standard Control Organization; in the paper, the term CDSCO encompasses both the Central Licence Approving Authority and the Drugs Controller, India / DCG(I); the Central Licence Approving Authority is defined in the Rules as the Drugs Controller, India
DCG(I)	Drugs Controller General (India), the officer who heads up the CDSCO; DCG(I) is the non-statutory term for “Drugs Controller, India”, the statutory term used in the legislation
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drugs Administration
FDC	Fixed dose combination
MHRA	Medicines and Healthcare Products Regulatory Agency
MNC	Multi-National Company
SDF	Single drug formulation
UK	United Kingdom
US	United States (of America)

Tables

Systemic Antibiotic Sales Volumes in India November 2007 – October 2012 (Millions of Units)	NOV07 - OCT08	NOV08 - OCT09	NOV09 - OCT10	NOV10 - OCT11	NOV11 - OCT12
TOTAL Antibiotic Sales (All FDCs + All SDFs)	2055.86m Units	2161.58m Units	2348.08m Units	2411.27m Units	2583.07m Units
All FDC formulations~ (% of total antibiotic sales)	632.78 (30.78%)	699.84 (32.38%)	750.66 (31.97%)	786.33 (32.61%)	872.02 (33.76%)
All SDF formulations (% of total antibiotic sales)	1423.08 (69.22%)	1461.74 (67.62%)	1597.43 (68.03%)	1624.93 (67.39%)	1711.04 (66.24%)
Sales arising from known* FDC Formulations (% of all FDC sales)	631.07m Units (99.73%)	697.67m Units (99.69%)	748.66m Units (99.73%)	784.52m Units (99.77%)	869.81m Units (99.75%)
Sales of CDSCO-Approved FDC Formulations (% of FDC known formulation sales)	334.83 (53.1%)	390.07 (56%)	445.69 (59.5%)	492.41 (62.8%)	569.55 (65.5%)
Sales of Unapproved FDC Formulations (% of FDC known formulation sales)	296.24 (46.9%)	341.02 (48.88%)	302.97 (40.5%)	292.11 (37.2%)	300.26 (34.5%)
Sales of FDC formulations approved by MHRA/EMA and/or FDA (% of FDC known formulation sales)	161.9 (25.7%)	192.6 (27.6%)	216.9 (29%)	237.8 (30.3%)	268.6 (30.9%)
Sales of Dual Antimicrobial FDC Formulations (% of FDC known formulation sales, % of total antibiotic sales)	408.72 (64.77%, 19.88%)	446.63 (64.02%, 20.66%)	442.53 (59.11%, 18.85%)	458.24 (58.41%, 19.00%)	488.55 (56.17%, 18.91%)
Sales arising from single drug formulations (SDFs)	1423.08m Units	1461.74m Units	1597.43m Units	1624.93m Units	1711.04m Units
Sales of CDSCO-Approved** SDFs (% of all SDF sales)	1384.81 (97.31%)	1422.60 (97.32%)	1556.63 (97.45%)	1586.60 (97.64%)	1670.17 (97.61%)
Sales of Unapproved Formulations (% of all SDF sales)	38.28 (2.69%)	39.15 (2.68%)	40.79 (2.55%)	38.34 (2.36%)	40.87 (2.39%)

Table 1: Systemic antibiotic sales volumes in India, November 2007 – October 2012, described by Total Sales, Sales of FDC and SDF formulations, Sales of FDC and SDF formulations with CDSCO-approval and with no record of approval and by Sales of dual anti-microbial FDC formulations; Sales are reported in millions of Units where a Unit is a strip of ten tablets or capsules or one bottle (oral liquid formulations) or one injection (parenteral drugs). ~ All systemic FDC formulations including those with full formulation information and combinations where only the antibiotic name was specified. *Known Formulations: Includes 118 FDCs for which complete formulation information was available in the PharmaTrac sales database and for which CDSCO approval could be determined; excludes 13 FDCs listed as 'combinations' with incomplete formulation details and for which CDSCO approval could not be determined; **CDSCO-approved/likely to be approved SDFs (see text).

Antibiotic FDCs: Top 20 formulations by volume of sales 2011-12	Dual Anti-microbial	Record of CDSCO approval	Approved MHRA /EMA and FDA	Listed NLEM 2011	Made by MNC	Volume Sold (Millions of Units)
AMOXYCILLIN + CLAVULANIC ACID	N	Y	Y/Y	Y	Y	161.8
AMPICILLIN + CLOXACILLIN	Y	N	Y/N	N	Y	110
TRIMETHOPRIM + SULFAMETHOXAZOLE	Y	Y	Y/Y	Y	Y	88.6
OFLOXACIN + ORNIDAZOLE	Y	Y	N/N	N	Y	63
CEFTRIAXONE + SULBACTAM	N	Y	N/N	N	Y	34.1
CEFIXIME + OFLOXACIN	Y	Y	N/N	N	Y	31.2
CEFTRIAXONE + TAZOBACTAM	N	Y	N/N	N	Y	31
FURAZOLIDONE + METRONIDAZOLE	Y	N	N/N	N	Y	30.4
NORFLOXACIN + METRONIDAZOLE	Y	N	N/N	N	Y	23.7
CEFPODOXIME + CLAVULANIC ACID	N	Y	N/N	N	Y	23.4
LOMOFEN (furazolidone/atropine/diphenoxylate)	N	N	N/N	N	N	20.9
OFLOXACIN + METRONIDAZOLE	Y	N	N/N	N	N	19.6
CEFIXIME + CLAVULANIC ACID	N	Y	N/N	N	Y	17.3
AMOXYCILLIN + CLOXACILLIN	Y	N	N/N	N	Y	16.8
CEFOTAXIME + SULBACTAM	N	Y	N/N	N	Y	16.2
PIPERACILLIN + TAZOBACTAM	N	Y	Y/Y	N	Y	16
CIPROFLOXACIN + TINIDAZOLE	Y	N	N/N	N	Y	15.8
CEFOPERAZONE + SULBACTAM	N	Y	N/N	N	Y	15.7
AMOXYCILLIN + CLOXACILLIN + LACTOBACILLUS	Y	Y	N/N	N	Y	10.7
CEFIXIME + LACTOBACILLUS	N	Y	N/N	N	Y	10.4
Proportion affirming	50%	65%	20%	10%	90%	
Top 20 FDC Volume (Millions of Units)						530.3m
Proportion of Total FDC volume (872.02m Units)						60.80%

Table 2: Top-selling 20 FDC antibiotic formulations by volume, 2011-12, according to dual antimicrobial formulation, regulatory approval status in India (CDSCO), UK (MHRA /EMA) and US (FDA), NLEM (India 2011) listing, Multinational Company (MNC) manufacture, and Volume sold. Y = Yes; N = No. Volume is expressed in Millions of Units where a Unit is a strip of ten 10 tablets or capsules or one bottle (oral liquid formulations) or one injection (parenteral drugs).

Antibiotic SDFs: Top 20 formulations by volume of sales 2011-12	Record of CDSCO approval	Approved MHRA / EMA and FDA	Listed NLEM 2011	Made by MNC	Volume Sold (Millions of Units)
CEFTRIAXONE	Y	Y/Y	Y	Y	146.1
CEFIXIME	Y	Y/Y	Y	Y	136.1
METRONIDAZOLE	Y	Y/Y	Y	Y	128.2
CEFOTAXIME	Y	Y/Y	Y	Y	125.7
AZITHROMYCIN	Y	Y/Y	Y	Y	119.2
AMIKACIN	Y	Y/Y	Y	Y	103.2
CEFPODOXIME	Y	Y/Y	N	Y	83.3
OFLOXACIN	Y	Y/N	Y	Y	72.9
GENTAMICIN	Likely	Y/Y	Y	Y	68.9
PENICILLIN G	Likely	Y/Y	N	Y	67.6
AMOXYCILLIN	Y	Y/Y	Y	Y	62.7
CEFADROXIL	Y	Y/Y	N	Y	59.1
OXYTETRACYCLINE	Y	Y/Y	N	Y	52.5
CIPROFLOXACIN	Y	Y/Y	Y	Y	51.7
LEVOFLOXACIN	Y	Y/Y	N	Y	45.9
TETRACYCLINE	Y	Y/Y	N	Y	36.4
ERYTHROMYCIN	Likely	Y/Y	Y	Y	35.6
CEFUROXIME	Y	Y/Y	N	Y	35.3
LINCOMYCIN	Y	Y/Y	N	Y	32.8
CEFALEXIN	Likely	Y/Y	Y	Y	31.3
Proportion affirming	100%	100% / 95%	60%	100%	
Top 20 SDF Volume (Millions of Units)					1494.3
Proportion of Total SDF Volume (1711.04m Units)					87.3%

Table 3: Top-selling 20 SDF antibiotics by volume, 2011-12, according to regulatory approval status in India (CDSCO), UK (MHRA /EMA) and US (FDA), NLEM (India 2011) listing, MNC manufacture, and Volume sold in 2011-12. Y = Yes; N = No. 'Likely' = likely to have CDSCO approval on basis of having export license, listed on NLEM, and/or marketed prior to CDSCO records commencing (1971). Volume is expressed in Millions of Units where a Unit is a strip of ten 10 tablets or capsules or one bottle (oral liquid formulations) or one injection (parenteral drugs).

Legends to Figures

Figure 1: FDC and single drug systemic antibiotic formulations listed on the market in India: Regulatory approval of FDC and single drug formulations (SDFs) in India (CDSCO), the UK (MHRA/EMA) and the USA (FDA), NLEM-India listing, proportions of FDC formulations comprised of dual antimicrobials, and proportions of FDC and single drug formulations made by MNC manufacturers. N = 118 FDCs and 86 SDFs.

Figure 2: Proportions of 12-monthly total antibiotic sales volumes (Units) annually, 2007-2012, comprised of FDC and single drug formulations (SDFs) and proportions of FDC and SDF sales volumes approved by the CDSCO, MHRA/EMA and FDA and NLEM-listed, and including dual antimicrobials. Volume is expressed in Millions of Units where a Unit is a strip of ten 10 tablets or capsules or one bottle (oral liquid formulations) or one injection (parenteral drugs).